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Busby, J., McMenamin, U., Spence, A., Johnston, B. T., Hughes, C., & Cardwell, C. (2018). Angiotensin receptor blocker use and gastro-oesophageal cancer survival: a population-based cohort study. *Alimentary Pharmacology and Therapeutics*, *47*(2), 279-288. https://doi.org/10.1111/apt.14388

Published in:
Alimentary Pharmacology and Therapeutics

Document Version:
Peer reviewed version

Queen's University Belfast - Research Portal:
Link to publication record in Queen's University Belfast Research Portal

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Authors: John Busby[1], Úna McMenamin[1], Andrew Spence[1], Brian T Johnston[2], Carmel Hughes[3], Chris R Cardwell[1]

[1] Centre for Public Health, Queen's University Belfast, Belfast, UK

[2]Belfast Health and Social Care Trust, Belfast, Northern Ireland, United Kingdom

[3]School of Pharmacy, Clinical and Practice Research Group, Queen's University Belfast

Running title: ARBs and gastro-oesophageal cancer survival

Correspondence: Dr. John Busby, Centre for Public Health, Queen's University Belfast, Institute for Clinical Science, Royal Victoria Hospital, Grosvenor Road, Belfast, BT12 6BJ, +442890971640, john.busby@qub.ac.uk

Manuscript word count (including references): 4,640

Summary word count: 244

Number of figures: 1

Number of tables: 3

Number of supplementary files: 4

Summary

Background: Angiotensin receptor blockers (ARBs; including candesartan, losartan, olmesartan and valsartan) are widely used to treat hypertension, heart failure and diabetic neuropathy. There is considerable preclinical evidence that ARBs can reduce cancer progression, particularly for gastric cancer. Despite this, epidemiological studies have yet to assess the impact of ARB use on gastro-oesophageal cancer survival.

Aim: To investigate the association between post-diagnosis ARB use and gastro-oesophageal cancer survival.

Methods: We selected a cohort of patients with newly-diagnosed gastro-oesophageal cancer between 1998 and 2012 from English cancer registries. We linked to prescription and clinical records from the Clinical Practice Research Datalink, and to death records from the Office for National Statistics. We used time-dependant Cox-regression models to calculate hazard ratios (HRs) comparing gastro-oesophageal cancer-specific mortality between post-diagnosis ARB users and non-users, after adjusting for demographics, comorbidities and post-diagnosis aspirin or statin use.

Results: Our cohort included 5,124 gastro-oesophageal cancer patients, of which 360 used ARBs, and 3,345 died due to their gastro-oesophageal cancer during follow-up. After adjustment, ARB users had moderately lower risk of gastro-oesophageal cancer mortality than the non-users (HR=0.83, 95% CI: 0.71, 0.98). There was evidence of a dose-response relationship with the lowest HRs observed among patients receiving at least two years of prescriptions (HR=0.42, 95% CI: 0.25, 0.72).

Conclusions: In this large population-based gastro-oesophageal cancer cohort, we found moderately reduced cancer-specific mortality among ARB users. However, confirmation in further independent epidemiological studies with sufficient staging information is required.

Introduction

Oesophageal and gastric cancer are among the most common cancers in the world, with around 456,000 and 952,000 new cases diagnosed annually.[1] Prognosis is extremely poor, even in developed countries such as the United Kingdom, where 55% of patients die within one year of diagnosis.[2] Those who survive suffer a marked reduction in their quality of life during treatment and recovery.[3, 4]

Angiotensin receptor blockers (ARBs; including candesartan, losartan, olmesartan and valsartan) are widely used and effective treatments for hypertension, heart failure and diabetic neuropathy.[5, 6] In England, ARBs are recommended as a first-line pharmacological treatment for hypertension patients aged under fifty-five or with comorbid diabetes,[7, 8] and nearly 20 million prescriptions are dispensed annually.[9] An estimated 200 million patients are treated with ARBs worldwide, representing 25% of all antihypertensive agents.[10] ARBs reduce blood pressure by blocking angiotensin II type I receptors within the renin-angiotensin system, however evidence of local expression of renin-angiotensin system components within cancer cells[11, 12] has fuelled debate that they might also affect cancer tumour development.[11, 13] In-vitro and mouse models at various cancer sites have shown that ARBs reduce tumour growth, stimulate cell apoptosis, reduce metastasis, and inhibit angiogenesis, suggesting that several chemopreventive mechanisms are possible.[14-18] More specifically, ARBs have been shown to slow proliferation, inhibit fibrosis, and prevent stress-induced injury in gastric cancer cell line and animal model studies.[19-23]

Despite convincing preclinical evidence that ARBs could influence cancer risk and progression, studies in humans are inconsistent. A meta-analysis of secondary outcomes from randomised controlled trials found little evidence of an association between ARB use and cancer risk[24], while a meta-analysis of observational studies reported reduced cancer risk among long-term ARB users.[25] Observational studies of cancer progression are fewer, but have found improved outcomes among ARB or angiotensin converting enzyme inhibitor (an alternative antihypertensive medication which

also inhibits the renin-angiotensin system) users across several cancer sites, while also highlighting methodological issues with the current literature such as poor generalisability, short follow-up, inadequate case-mix adjustment and potential exposure misclassification.[26, 27] To date, no studies have investigated ARB use and gastro-oesophageal mortality, although olmesartan has been shown to cause severe enteropathy in some patients, suggesting upper-gastrointestinal effects.[28] Consequently, we used a large population-based dataset from the UK to robustly assess this association.

Methods

Data Sources

Our study used data from the English National Cancer Data Repository, linked to GP records from the UK Clinical Practice Research Datalink, deprivation indices from census information, and death registration data from the Office for National Statistics . The National Cancer Data Repository holds UK-wide data from English cancer registries compiled from general practices, National Health Service and private hospitals, and death certificates. It contains detailed information about the patient's cancer, including year of diagnosis, stage, histologic grade, tumour type (adenocarcinoma or squamous cell carcinoma) and treatment (surgery, chemotherapy, and radiotherapy). The Clinical Practice Research Datalink contains computerised medical records from 674 general practices (approximately 7% of the UK population) which are audited for data completeness and quality. Practices meeting a predefined quality threshold are deemed 'up to standard' and included in future extracts. Data recorded within the Clinical Practice Research Datalink include patient demographics, clinical diagnoses (using Read codes) and prescription medication use. Previous research has found prescription and clinical information to be of high quality.[29] Office for National Statistics death-registration data provide details on the date and cause(s) of death.

Ethical approval for all purely observational research using anonymised Clinical Practice Research Datalink data was obtained from a National Research Ethics Service Committee. The protocol for this study was approved by the Clinical Practice Research Datalink Independent Scientific Advisory Committee (Ref: 15_096R), and has been made available to reviewers.

Study Design and Population

We identified a cohort of patients with newly-diagnosed gastro-oesophageal cancer from English cancer registry records (ICD-10 codes C15 or C16) between 1998 and 2012. Cohort members with a

previous diagnosis of cancer (excluding non-melanoma skin cancer) were identified and excluded using a list of cancer Read codes modified for use in the Clinical Practice Research Datalink.[30] Patients were excluded if they were diagnosed: (a) before they were registered with a Clinical Practice Research Datalink practice, (b) before their practice was deemed up to research standard, (c) after they left a Clinical Practice Research Datalink practice, or (d) after data were last collected from their practice by the Clinical Practice Research Datalink. A small number of patients had more than one gastro-oesophageal cancer record in the National Cancer Data Repository; when this occurred we used their first record.

Deaths were identified from Office for National Statistics records, and gastro-oesophageal cancer specific deaths were defined as those with an underlying cause of gastro-oesophageal cancer (ICD-10 codes C15, C16 or C26). Patients with less than six months follow-up were excluded as it is unlikely that these could be influenced by post-diagnosis medication use. Therefore the follow-up period started from six months after diagnosis. The end of follow-up was the earliest date of: death, end of registration with the practice, last collection of data from the practice, or end of death record follow-up.

Definition of exposure

We used the British National Formulary[31] to compile a list of proprietary and generic medication names to identify ARB use (Appendix 1). We added a lag of six months to ARB use as these medications are unlikely to have an immediate effect on gastro-oesophageal cancer progression, and to prevent reverse causation.[32, 33] A diagram illustrating our design is shown in Appendix 2. We defined patients as users after they received their first prescription during the exposure period. To enable the testing of dose-response relationships we extracted data on the number of tablets and medication strength, and calculated defined daily doses (DDDs). The DDD system is a validated measure of drug consumption maintained by the World Health Organisation. A single DDD is the

average maintenance dose per day of a drug used for its main indication in adults (e.g. hypertension for ARBs). There was insufficient information to calculate DDDs for 0.1% of prescriptions, and implausible values were recorded in a further 0.1%. In these cases we assumed the most common DDD based on other prescriptions with complete information. We calculated a running DDD total for each patient and identified the day when patients received their 1st (first use), 183th (six months' use), 365th (one year's use) and 730th (two years' use) DDDs.

Covariates

Patients' age, smoking (current, former, never), units of alcohol consumed per week (0,1-14, 15-28, 29-42, 43+), and body mass index (BMI; underweight [BMI<18.5], normal weight [18.5≤BMI<25], overweight [25≤BMI<30] and obese [BMI≥30]) data were determined from the closest GP record before gastro-oesophageal cancer diagnosis (values more than 10 years before diagnoses were discarded). We used GP records to identify pre-diagnosis comorbidities (cerebrovascular disease, chronic pulmonary disease, congestive heart disease, diabetes, liver disease, myocardial infarction, peptic ulcer disease, peripheral vascular disease, renal disease) using a list of Read codes modified for use in the Clinical Practice Research Datalink.[30] Deprivation data were available from census information, and based on the 2010 Index of Multiple Deprivation score of the patient's postcode. We used Clinical Practice Research Datalink prescription records to identify patients using statins or aspirin after diagnosis, as these have been shown to influence cancer progression previously.[34, 35]

Statistical analysis

We calculated descriptive statistics and compared the demographic, lifestyle and clinical characteristics of the ARB users and non-users. We produced survival graphs using the Simon–Makuch method, which is an alternative to the Kaplan-Meier but appropriately accounts for time-varying covariates.[36] We used time-dependant Cox regression models to calculate hazard ratios (HRs) comparing gastro-oesophageal cancer-specific death between ARB users and non-users. We

conducted analyses for gastro-oesophageal cancer, and separately for oesophageal (ICD-10 code C15) and gastric (ICD-10 code C16) cancer. In our primary analysis we included ARB use as a time-varying covariate to avoid immortal time bias.[37] Therefore patients were initially included within the analysis as non-users until six months after their first use (due to the exposure lag), after which they were included as users until the end of follow-up. Our primary analysis adjusted for age at diagnosis, year of diagnosis (separate term for each year), deprivation quintile, comorbidities (separate terms for each), post-diagnosis use of aspirin or statins (using time-varying covariates and a six month lag after their first prescription), cancer site (gastric or oesophageal), and treatment within six months of diagnosis (separate terms for surgery, chemotherapy, radiotherapy). We repeated our analysis by number of DDDs prescribed (e.g. patients were included in the 1-364 DDD group until six months after they received their 365th DDD), and for candesartan and losartan, the most commonly prescribed ARBs.[9] Again, the use of time-varying covariates negates immortal time bias. We conducted interaction tests to assess differences by tumour type.

Sensitivity and subgroup analyses

We conducted sensitivity analysis for all-cause mortality, and for cause-specific mortality where deaths with a secondary cause (i.e. listed as an 'other cause of death' on death certificate) of gastro-oesophageal cancer were included. We also conducted sensitivity analyses with a lag period of zero (patients followed-up from diagnosis) and twelve months (patients followed-up from twelve months after diagnosis). We performed two simplified analyses which controlled for immortal time bias without time-varying covariates.[37] Firstly, we based ARB usage on the six months after diagnosis, and followed-up patients from six months after diagnosis. Secondly, we investigated ARB usage in the year prior to diagnosis, and followed-up patients from the date of diagnosis. Diagrams illustrating the design of our sensitivity analyses which vary the exposure lag and/or period are given in Appendix 2. We conducted subgroup analysis by tumour type (i.e. adenocarcinoma and squamous cell carcinoma), as these differ in incidence, risk factors and pathogenesis. We also carried out sub-

group analysis restricted to patients receiving surgery, as they are likely to form a more homogenous group of earlier-stage patients.

To assess if confounding by indication was driving our results, we conducted three further sensitivity analyses restricted to patients with similar clinical diagnoses. First, we restricted our analysis to patients with a hypertension diagnosis (Read code categories G20 and 662) in the year prior to cancer diagnosis. Second, we restricted our analysis to patients who received an antihypertensive medication (diuretics, vasodilator antihypertensive drugs, centrally acting antihypertensive drugs, alpha-adrenoceptor blocking drugs, beta-blockers, angiotensin converting enzyme [ACE] inhibitors, ARBs, renin inhibitors, and calcium channel blockers) in the year prior to cancer diagnosis. Third, we compared patients who received ARBs to those who received a different antihypertensive medication after diagnosis (using a time-varying covariate), as the use of an active comparison can overcome several common pharmacoepidemiological biases.[38] Similarly, we conducted negative control analyses[39] for ACE inhibitors as they have similar indications to ARBs, but a distinct biological mechanism within the renin-angiotensin system. Therefore, if confounding was driving our ARB analyses we would expect to see similar associations for ACE inhibitors. Conversely, findings of a substantial association for ARBs, which are not replicated among the negative controls, would support a causal interpretation.

We performed additional sensitivity analysis adjusting for tumour prognostic features (stage, grade) and patient lifestyle factors (smoking, alcohol consumption, BMI) using multiple imputation with chained equations. Briefly, this is a simulation-based approach for handling missing data which leads to valid statistical inferences under certain assumptions.[40] The imputation used ordered logit models with age, deprivation, death indicator and the baseline hazard function as covariates. Lastly, we used the Fine and Gray sub-distribution hazard model to assess the impact of competing risks from non-gastro-oesophageal cancer deaths.[41]

Results

Cohort Description

We identified 9,714 gastro-oesophageal cancer cases with no prior cancer diagnosis registered at Clinical Practice Research Datalink practices. We excluded 4,590 patients as they had either less than six months follow-up (n=4,582) or a duplicate record in the National Cancer Data Repository (n=8), leaving 5,124 patients for analysis. Median follow-up was 1.4 years (maximum 17.2 years). ARB users were more likely to be female, have comorbidities (particularly diabetes, renal disease and congestive heart disease), be treated with statins or aspirin after diagnosis, undergo surgery, be non- or ex- smokers, and be obese (Table 1).

Association between ARB use and survival

Overall, ARB users were at a moderately lower risk of gastro-oesophageal cancer death than non-users both before (unadjusted HR=0.80, 95% CI: 0.69, 0.94; Figure 1) and after adjustment for demographics, comorbidities, cancer treatments and post-diagnosis aspirin or statin use (adjusted HR=0.83, 95% CI: 0.71, 0.98; Table 2). There was evidence of a dose-response relationship (p-value for trend=0.003); the largest differences in mortality were found among those who had received at least 730 DDDs (adjusted HR=0.42, 95% CI: 0.25, 0.72), although associations were relatively similar for those receiving 1-182, 183-364, 365-729 DDDs. We observed broadly similar estimates for losartan (adjusted HR=0.84, 95% CI: 0.59, 1.21) and candesartan (adjusted HR=0.73, 95% CI: 0.49, 1.09). We found slightly stronger association among patients with gastric (adjusted HR=0.79, 95% CI: 0.62, 1.00) than oesophageal (adjusted HR=0.89, 95% CI: 0.71, 1.10) cancer, although the dose-response patterns were comparable to the combined analysis, with very large decreases in cancer-specific mortality among both oesophageal (adjusted HR=0.44, 95% CI: 0.21, 0.94) and gastric (adjusted HR=0.40, 95% CI: 0.19, 0.84) patients receiving at least 730 DDDs of ARBs. The full results of the gastro-oesophageal model are given in Appendix 3.

Sensitivity and subgroup analyses

Our results were similar in the simpler analysis basing ARB use on the year prior, or six-months after diagnosis (Table 3). Our conclusions were unchanged when expanding our cancer-specific death definition to include secondary death causes, and for all-cause mortality. Our results were robust to alterations in the exposure lag period from zero to twelve months, and did not change appreciably when adjusting for tumour prognostic features (i.e. stage, grade), or patient lifestyle factors (i.e. smoking, alcohol, BMI) using multiple imputation methods.

We observed broadly similar hazard ratios when restricting our analysis to patients who received surgical treatment (adjusted HR=0.81; 95% CI: 0.63, 1.05), or with a prior diagnosis of hypertension (adjusted HR=0.83; 95% CI: 0.62, 1.09). Likewise, our results were broadly similar when restricting to those in receipt of antihypertensive medications before diagnosis (adjusted HR=0.80; 95% CI: 0.67, 0.94), or when comparing ARB users to patients receiving a different antihypertensive medication after gastro-oesophageal cancer diagnosis (adjusted HR=0.83; 95% CI: 0.71, 0.98). We did not find any evidence of an association between ACE inhibitor use and gastro-oesophageal survival (adjusted HR: 0.98, 95% CI: 0.89, 1.08; Appendix 4). The association between ARB use and cancer-mortality was slightly stronger for patients with adenocarcinoma (adjusted HR=0.78, 95% CI: 0.65, 0.94) than squamous cell carcinoma (adjusted HR=0.95, 95% CI: 0.63, 1.43), although this difference was not statistically significant (p-value for interaction=0.52).

Discussion

Summary of main findings

In this large, population-based cohort of newly-diagnosed gastro-oesophageal cancer patients, we found a statistically significant reduction of 17% in cancer-specific morality among ARB users after adjustment for patient demographics, comorbidities, cancer treatments and post-diagnosis aspirin or statin use. There was some evidence of a dose-response relationship with the largest decreases in mortality observed among patients receiving at least 2 years' worth of prescriptions.

Strengths and weaknesses

This is the first study to investigate ARB use and survival from gastro-oesophageal cancer. Our study is based on a high-quality population-based cohort of patients with registry-confirmed gastro-oesophageal cancer which was followed-up for up to 17 years.[29] Linkage to Office for National Statistics death registration data allowed robust verification of death, and facilitated a gastro-oesophageal cancer-specific analysis, which should be more sensitive to small changes in disease-specific mortality, and less susceptible to confounding by indication than all-cause deaths.[33, 42] Although some misclassification of death cause is possible, studies have shown this is likely to have a limited impact on our estimates (as there is no obvious mechanism for differential misclassification)[43], and our results were similar when including deaths where gastro-oesophageal cancer was not the underlying cause. We used prescribing data collected as part of routine clinical care which accurately reflects GP prescribing practices and negates the risk of recall bias. These data also included detailed information on the type of ARB, and the strength, quantity and timing of prescription, which allowed us to investigate dose-response relationships, and conduct separate analyses for specific medications. ARBs are not available over-the-counter in the UK, which negates exposure misclassification due to over-the-counter usage.

Our study had several potential weaknesses. We necessarily excluded patients who lived for less than six months after diagnosis, therefore our results cannot be applied to those with a very poor prognosis. Our study is observational and hence open to confounding by incomplete or unmeasured covariates. Although we have adjusted for several key determinants of gastro-oesophageal cancer survival (e.g. age, comorbidities and cancer treatments), some were incompletely recorded (e.g. smoking history) and others were not available within our dataset (e.g. ethnicity and family history). The lack of complete information on cancer stage is of particular concern, especially as ARB users were more frequently diagnosed with lower-stage cancers than non-users (e.g. 16.9% vs. 9.4% stage 1). It is also possible that our study could be subject to a 'healthy user effect' whereby patients who receive one preventative therapy (ARBs) are more likely to use other therapies (e.g. endoscopy), or more closely follow medical advice (e.g. attend medical appointments).[44]

Nevertheless, the findings from our sensitivity analyses suggest that confounding or missing data issues were not solely driving our results. For example, the protective association for ARBs was preserved when using other antihypertensive medications as an active comparator, when restricting to those who received surgery (who should form a more homogeneous cohort of lower-stage patients), and when limiting our analysis to patients with a prior hypertension diagnosis. Similarly, we observed little evidence of an association between gastro-oesophageal cancer mortality and ACE inhibitor use, which have similar indications to ARBs. Lastly, our conclusions were unchanged when using multiple imputation to adjust for cancer stage and grade, albeit this analysis is particularly sensitive to departures from the 'missing at random' assumption due to the large proportion of missing data for these variables.[45] We do not know if patients adhered to their prescribed medications, however our main conclusions were similar when restricting our analysis to patients who received multiple ARB prescriptions (≥730 DDDs), where non-compliance is less of a concern. Finally, ARBs were one of six medications investigated within a broader programme of work, meaning that multiple testing could be a potential concern.

Comparison with the previous literature

We are unaware of any other studies comparing gastro-oesophageal cancer mortality between ARB users and non-users. Several studies have previously investigated the role of renin-angiotensin system blockade on cancer survival. However they have generally combined ACE inhibitors with ARBs[27], potentially obfuscating the therapeutic effect of each medication as they have distinct mechanisms of action within the renin-angiotensin system, and are known to differ in their side effect profiles. Our finding of a much stronger association with gastro-oesophageal survival among ARB than ACE inhibitor users could suggest that separate analyses are indeed preferable.

Nevertheless, our results are consistent with findings of longer survival among gastro-oesophageal cancer patients using renin-angiotensin system blockade medications in two other studies based in Taiwan and Korea.[46, 47] However, each of these were substantially limited by poor generalisability (e.g. restricted to advanced gastric cancer), an inability to identify cancer-specific deaths, inappropriate statistical methods (e.g. chi-squared test) and small sample size (196 patients in total). Our study improves on the current literature by using appropriate methodology to analyse a population-based cohort over thirty times larger than previous work. Our results are also consistent with the findings from several other observational studies reporting improved survival among renin-angiotensin system blockade medication users at other sites.[26, 27] For example, one recent meta-analysis found that mortality was 25% (95% CI: 1, 43) lower among cancer patients using ACE inhibitors or ARBs, with particularly large decreases in urinary tract, colorectal, pancreatic, and prostate cancer.[27]

Implications for practitioners and researchers

Our results provide epidemiological evidence that the use of ARBs may be associated with improved gastro-oesophageal cancer survival. Our conclusions are consistent with preclinical research which

has demonstrated that ARBs can slow tumour growth, stimulate cell apoptosis, reduce metastasis, and inhibit angiogenesis.[14-18] More specifically, ARBs have been shown to slow proliferation, inhibit fibrosis, and prevent stress-induced injury in gastric cancer cell line and animal model studies.[19-23] Our finding of a slightly stronger association among gastric than oesophageal cancer patients requires further exploration, however it could be due to higher renin-angiotensin system expression among patients with *H.pylori* infection[48], the most important risk factor for gastric cancer. Likewise our finding of a slightly stronger association for adenocarcinoma than squamous cell carcinoma could be due to ARBs promoting healing of reflux oesophagitis among proton pump inhibitor users.[49]

Our study suggests that it is worth further exploring the potential for ARBs to be repurposed as a gastro-oesophageal cancer treatment, particularly as they are inexpensive (losartan costs £1.15 [$1.48] per 28-tablet pack)[50], have no major safety concerns[51], and are well tolerated by patients.[52] In this paper we have demonstrated that the association with gastro-oesophageal cancer mortality adheres to several of Hill's criteria for causation including biological plausibility, experimental evidence, temporality, biological gradient, consistency and specificity.[53] However, these findings should be replicated in independent epidemiological studies with more complete information on cancer stage.

Conclusions

In this large population-based cohort of patients with registry-confirmed gastro-oesophageal cancer, we found a 17% reduction in cancer-specific mortality among ARB users. Although this association adheres to several of Hill's criteria for causation, and is consistent with preclinical evidence, further independent epidemiological studies with more complete stage data is required.

Disclosures

Acknowledgements: This study is based in part on data from the Clinical Practice Research Datalink obtained under licence from the UK Medicines and Healthcare products Regulatory Agency. However, the interpretation and conclusions contained in this study are those of the author/s alone. Access to the Clinical Practice Research Datalink dataset was funded by a Clinical Research Bursary for AS from Cancer Research-UK [C54914/A20558].

Abbreviations: ACE: angiotensin converting enzyme**;** ARB: angiotensin receptor blocker; BMI: body mass index; DDD: defined daily dose; HR: hazard ratio

Authorship Statement: CC, AS, BJ and CH conceived the study. JB conducted the analysis and drafted the initial manuscript. All authors critically revised the article for intellectual content and approved the final manuscript. JB acts as the study guarantor.

Conflict of interest: None to declare

Figure Legends

Figure 1: Red line represents the proportion of ARB users that are alive at a given time after diagnosis. Blue line represents the proportion of non-ARB users that are alive at a given time after diagnosis.

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Tables and Figures

Table 1: Patient characteristics by ARB use at any time after diagnosis

	Non-user	User
Number of Patients	4,764	360
Year of Diagnosis		
1998-2002	1,163 (24.4%)	38 (10.6%)
2003-2007	1,651 (34.7%)	120 (33.3%)
2008-2012	1,950 (40.9%)	202 (56.1%)
Age at Diagnosis (SD)	69.5 (11.9)	71.9 (9.3)
0-49	268 (5.6%)	3 (0.8%)
50-59	684 (14.4%)	33 (9.2%)
60-69	1,284 (27.0%)	104 (28.9%)
70-79	1,512 (31.7%)	149 (41.4%)
80+	1,016 (21.3%)	71 (19.7%)
Gender		
Male	3,243 (68.1%)	216 (60.0%)
Female	1,521 (31.9%)	144 (40.0%)
Deprivation Quintile		
1 (Least Deprived)	949 (19.9%)	74 (20.6%)
2	1,182 (24.8%)	90 (25.0%)
3	951 (20.0%)	71 (19.7%)
4	955 (20.1%)	78 (21.7%)
5 (Most Deprived)	723 (15.2%)	47 (13.1%)
Missing	4	0
Comorbidities		
Diabetes	535 (11.2%)	101 (28.1%)
Chronic pulmonary disease	572 (12.0%)	57 (15.8%)
Renal disease	347 (7.3%)	65 (18.1%)
Cerebrovascular disease	242 (5.1%)	18 (5.0%)
Peptic ulcer disease	231 (4.8%)	18 (5.0%)
Peripheral vascular disease	218 (4.6%)	25 (6.9%)
Myocardial infarction	172 (3.6%)	26 (7.2%)
Congestive heart disease	168 (3.5%)	30 (8.3%)
Liver Disease	22 (0.5%)	4 (1.1%)
Confounder Medications		
Statin	1,149 (24.1%)	198 (55.0%)
Aspirin	931 (19.5%)	154 (42.8%)
Treatment		
Surgery	2,128 (44.7%)	186 (51.7%)
Chemotherapy	2,028 (42.6%)	160 (44.4%)
Radiotherapy	805 (16.9%)	64 (17.8%)
Grade		
1	183 (5.2%)	15 (5.9%)
2	1,398 (39.8%)	109 (42.7%)
3	1,900 (54.0%)	129 (50.6%)
4	35 (1.0%)	2 (0.8%)
Missing	1,248	105
Tumour type		
Adenocarcinoma	3,275 (68.7%)	265 (73.8%)
Squamous	804 (16.9%)	45 (12.5%)
Other	685 (14.4%)	49 (13.6%)
Stage		
1	73 (9.4%)	11 (16.9%)
2	147 (19.0%)	13 (20.0%)

3	280 (36.2%)	25 (38.5%)
4	274 (35.4%)	16 (24.6%)
Missing	3,990	295
Smoking		
Never	1,707 (39.4%)	156 (45.0%)
Former	1,557 (35.9%)	160 (46.1%)
Current	1,069 (24.7%)	31 (8.9%)
Missing	431	13
Alcohol (units per week)		
None	821 (30.1%)	71 (30.5%)
1-14	1,366 (50.0%)	117 (50.2%)
15-28	336 (12.3%)	31 (13.3%)
29-42	115 (4.2%)	10 (4.3%)
43+	94 (3.4%)	4 (1.7%)
Missing	2,032	127
BMI (kg/m^2)		
Underweight (<18.5)	152 (4.4%)	2 (0.6%)
Normal (18.5-24.9)	1,239 (36.0%)	80 (25.4%)
Overweight (25-29.9)	1,352 (39.3%)	132 (41.9%)
Obese (≥30)	698 (20.3%)	101 (32.1%)
Missing	1,323	45

Table 2: Association between ARB use and gastro-oesophageal cancer mortality

	N	Person-Years	Deaths	Unadjusted HR	Adjusted HR[a]	Trend p-value
Gastro-oesophageal						
All ARBs Combined						
Never	4,764	9,241	3,175	Ref	Ref	0.003
Ever	360	786	170	0.80 (0.69,0.94)	0.83 (0.71,0.98)	
1-182 DDDs	146	263	92	0.87 (0.71,1.07)	0.91 (0.74,1.13)	
183-364 DDDs	67	130	40	0.92 (0.67,1.25)	0.97 (0.71,1.33)	
365-729 DDDs	57	109	24	0.82 (0.55,1.23)	0.83 (0.55,1.25)	
730+ DDDs	90	284	14	0.42 (0.25,0.71)	0.42 (0.25,0.72)	
Losartan						
Never	4,973	9,698	3,278	Ref	Ref	
Ever	151	330	67	0.82 (0.64,1.04)	0.82 (0.64,1.06)	
Candesartan						
Never	5,013	9,772	3,300	Ref	Ref	
Ever	111	255	45	0.72 (0.54,0.97)	0.71 (0.52,0.95)	
Oesophageal						
All ARBs Combined						
Never	2,565	4,499	1,776	Ref	Ref	0.135
Ever	168	338	91	0.89 (0.72,1.09)	0.89 (0.71,1.10)	
1-182 DDDs	68	100	47	0.87 (0.65,1.16)	0.89 (0.66,1.19)	
183-364 DDDs	31	53	24	1.21 (0.80,1.81)	1.21 (0.80,1.81)	
365-729 DDDs	30	53	13	0.95 (0.55,1.65)	0.92 (0.53,1.59)	
730+ DDDs	39	133	7	0.46 (0.22,0.97)	0.44 (0.21,0.94)	
Losartan						
Never	2,667	4,698	1,836	Ref	Ref	
Ever	66	139	31	0.82 (0.58,1.17)	0.84 (0.59,1.21)	
Candesartan						
Never	2,681	4,732	1,842	Ref	Ref	
Ever	52	105	25	0.76 (0.52,1.14)	0.73 (0.49,1.09)	
Gastric						
All ARBs Combined						
Never	2,199	4,743	1,399	Ref	Ref	0.009
Ever	192	448	79	0.75 (0.60,0.94)	0.79 (0.62,1.00)	
1-182 DDDs	78	163	45	0.89 (0.66,1.21)	0.95 (0.70,1.28)	
183-364 DDDs	36	78	16	0.70 (0.43,1.15)	0.75 (0.46,1.24)	
365-729 DDDs	27	56	11	0.74 (0.41,1.34)	0.76 (0.42,1.39)	
730+ DDDs	51	151	7	0.40 (0.19,0.85)	0.40 (0.19,0.84)	
Losartan						
Never	2,306	5,000	1,442	Ref	Ref	
Ever	85	191	36	0.85 (0.61,1.18)	0.81 (0.57,1.14)	
Candesartan						
Never	2,332	5,041	1,458	Ref	Ref	
Ever	59	150	20	0.68 (0.44,1.06)	0.67 (0.43,1.05)	

[a] Adjusted for age, deprivation, year of diagnosis, cancer site, cancer treatment within 6 months (radiotherapy, chemotherapy, surgery), comorbidities (cerebrovascular disease, chronic pulmonary disease, congestive heart disease, diabetes, liver disease, myocardial infarction, peptic ulcer disease, peripheral vascular disease, renal disease) and other medication use (statins and aspirin, time-varying after diagnosis)

Figure 1: Association between ARB use and gastro-oesophageal cancer mortality

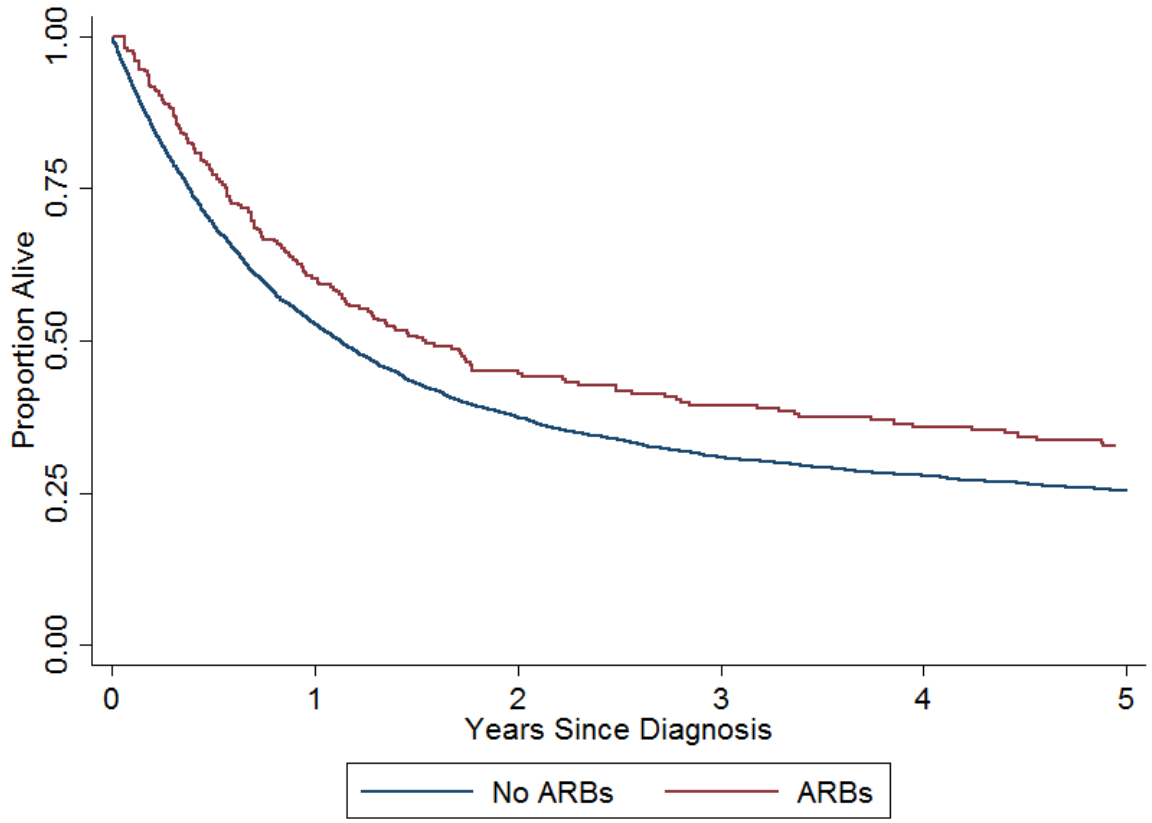


Table 3: Sensitivity and subgroup analysis for ARB use and gastro-oesophageal cancer mortality

	Non-Users[a]			Users			Unadjusted HR	Adjusted HR[c]
	N	Person-Years	Deaths[b]	N	Person-Years	Deaths		
Main analysis	4,764	9,241	3,175	360	786	170	0.80 (0.69,0.94)	0.83 (0.71,0.98)
Death definition								
All-cause	4,764	9,241	3,605	360	786	214	0.87 (0.76,1.00)	0.87 (0.75,1.00)
Primary or secondary GO cause	4,764	9,241	3,350	360	786	189	0.84 (0.73,0.98)	0.86 (0.74,1.00)
Exposure definition								
Year before diagnosis	4,757	11,733	3,130	367	821	215	0.91 (0.79,1.04)	0.91 (0.79,1.05)
Six months after diagnosis	4,804	9,447	3,167	320	581	178	0.82 (0.71,0.96)	0.85 (0.73,1.00)
Exposure lag								
None	4,731	11,579	3,149	393	976	196	0.82 (0.71,0.95)	0.85 (0.73,0.99)
12 months	4,870	7,314	1,722	254	629	94	0.81 (0.66,1.00)	0.82 (0.66,1.02)
Tumour type[d]								
Adenocarcinoma	3,275	6,486	2,196	265	596	125	0.79 (0.66,0.94)	0.78 (0.65,0.94)
Squamous cell carcinoma	804	1,305	552	45	78	28	0.98 (0.67,1.43)	0.95 (0.63,1.43)
Surgical treatment	2,128	5,817	1,233	186	527	71	0.83 (0.66,1.06)	0.81 (0.63,1.05)
Hypertension diagnosis / treatment								
Pre-diagnosis hypertension diagnosis[e]	731	1,168	499	116	214	61	0.85 (0.65,1.12)	0.83 (0.62,1.09)
Pre-diagnosis antihypertensive medication users[f]	2,324	3,888	1,565	335	724	161	0.74 (0.63,0.87)	0.80 (0.67,0.94)
ARB vs. other antihypertensive medication[g]	4,764	9,241	3,175	360	786	170	0.80 (0.69,0.94)	0.83 (0.71,0.98)
Multiple Imputation								
Lifestyle factors[h]	4,764	9,241	3,175	360	786	170	0.80 (0.69,0.94)	0.85 (0.73,1.00)
Tumour prognostic factors[i]	4,764	9,241	3,175	360	786	170	0.80 (0.69,0.94)	0.87 (0.73,1.04)
Lifesyle & tumour prognostic factors[j]	4,764	9,241	3,175	360	786	170	0.80 (0.69,0.94)	0.87 (0.73,1.03)
Competing risks regression[k]	4,764	9,241	3,175	360	786	170	0.80 (0.69,0.93)	0.84 (0.72,0.99)

[a] Non-users for each sensitivity analysis except for 'ARB vs. other antihypertensive medication' where patients who received a different antihypertensive medication serve as the non-user group

[b] Deaths with an underlying cause of gastro-oesophageal cancer unless otherwise stated

[c] Adjusted for age, deprivation, year of diagnosis, cancer site, cancer treatment within 6 months (radiotherapy, chemotherapy, surgery), comorbidities (cerebrovascular disease, chronic pulmonary disease, congestive heart disease, diabetes, liver disease, myocardial infarction, peptic ulcer disease, peripheral vascular disease, renal disease) and other medication use (statins, aspirin, time-varying after diagnosis)

[d] P-value for interaction: 0.518

[e] Restricted to patients with a hypertension diagnosis (Read code categories G20 and 662) in the year prior to diagnosis

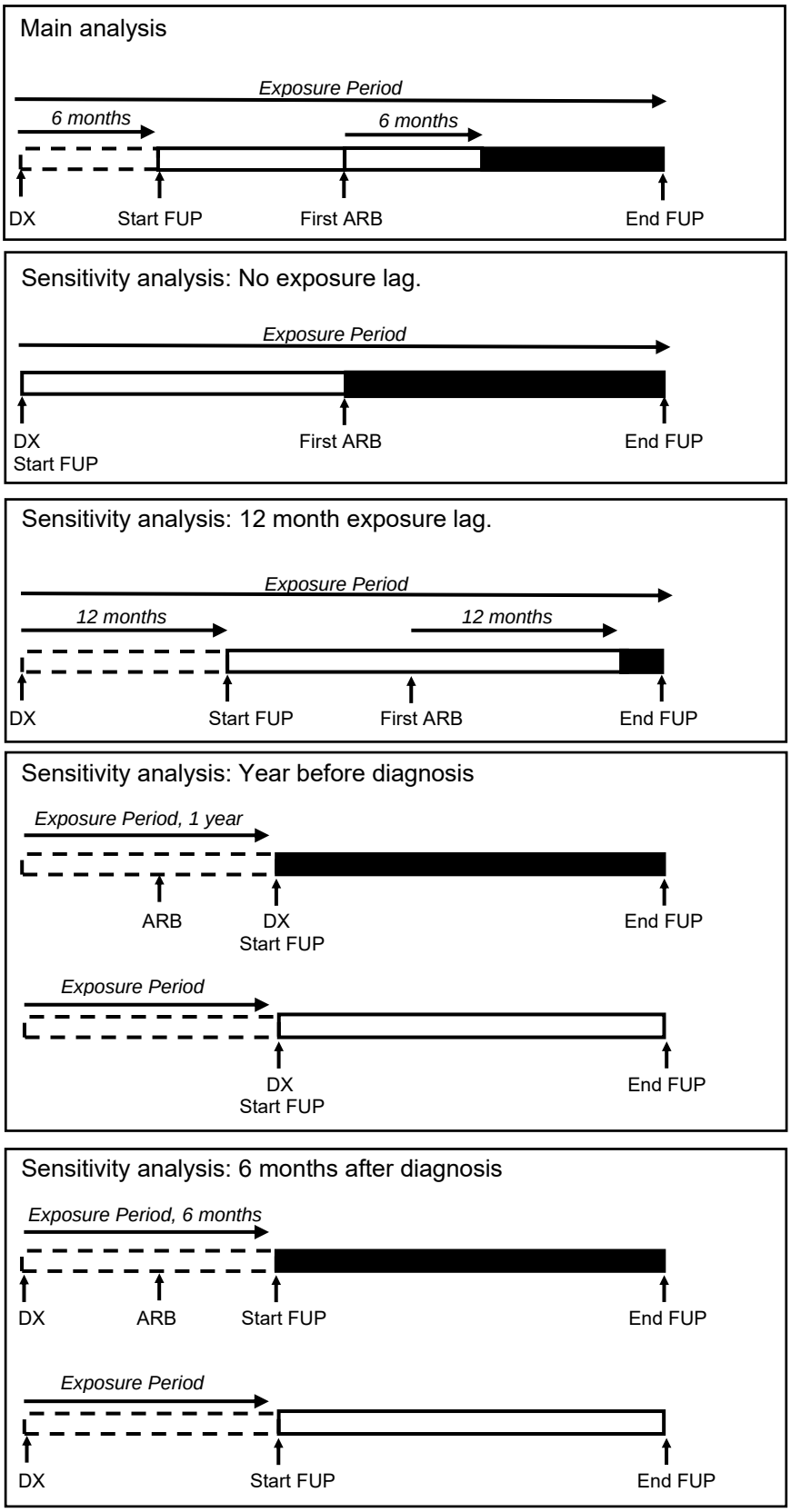
[f] Restricted to patients with a prescription of any antihypertensive medication (diuretics, vasodilator antihypertensive drugs, centrally acting antihypertensive drugs, alpha-adrenoceptor blocking drugs, beta-blockers, ACEIs, ARBs, renin inhibitors, and calcium channel blockers) in the year prior to cancer diagnosis
[g] Using other antihypertensive medications as an active comparator
[h] Additionally adjusted for smoking, BMI and alcohol consumption
[i] Additionally adjusted for stage and grade
[j] Additional adjusted for smoking, BMI, alcohol consumption, stage and grade
[k] Using the Fine and Gray sub distribution hazard model with non-gastro-oesophageal cancer death as competing risk

Appendices

Appendix 1: List of generic and proprietary drug names used to identify ARBs

Substance	Medication
Azilsartan Medoxomil	Azilsartan, Edarbi (Takeda, High Wycombe, UK)
Candesartan Cilexetil	Candesartan, Amias (Takeda, High Wycombe, UK)
Eprosartan	Eprosartan, Teveten (Abbott Healthcare, Maidenhead, UK)
Irbesartan	Irbesartan, Aprovel (Bristol-Myers Squibb, New York, US & Sanofi-Aventis, Gentilly, France), Coaprovel (Bristol-Myers Squibb, New York, US & Sanofi-Aventis, Gentilly, France)
Losartan Potassium	Losartan, Cozaar (MSD, Hertfordshire, UK)
Olmesartan Medoxomil	Olmesartan, Olmetec (Daiichi Sankyo, Tokyo, Japan), Sevikar (Daiichi Sankyo, Tokyo, Japan)
Telmisartan	Telmisartan, Micardis (Boehringer Ingelheim, Rhein, Germany)
Valsartan	Valsartan, Diovan (Novartis, Basal, Switzerland), Entresto (Novartis, Basal, Switzerland)

Appendix 2: Illustration of study design for selected analyses[a]



Legend: Before FUP ARB User ARB Non-user

[a] FUP: follow-up period; DX: breast cancer diagnosis

Appendix 3: Complete model results for fully-adjust gastro-oesophageal analysis

Covariate	HR (95% CI)
ARB use	
Never	Ref
Ever	0.83 (0.71,0.98)
Age at Diagnosis	1.02 (1.01,1.02)
Deprivation Quintile	
1 (Least Deprived)	Ref
2	1.07 (0.96,1.18)
3	1.02 (0.92,1.14)
4	1.06 (0.95,1.18)
5 (Most Deprived)	1.11 (0.99,1.25)
Year of Diagnosis	
1998	Ref
1999	0.85 (0.66,1.11)
2000	0.96 (0.76,1.22)
2001	0.77 (0.62,0.97)
2002	0.81 (0.65,1.01)
2003	0.78 (0.62,0.97)
2004	0.69 (0.55,0.86)
2005	0.78 (0.62,0.97)
2006	0.72 (0.58,0.90)
2007	0.67 (0.54,0.84)
2008	0.72 (0.58,0.90)
2009	0.55 (0.43,0.69)
2010	0.54 (0.43,0.68)
2011	0.59 (0.46,0.74)
2012	0.64 (0.51,0.81)
2013	0.55 (0.42,0.71)
Treatment	
Surgery	0.54 (0.50,0.58)
Chemotherapy	1.36 (1.26,1.47)
Radiotherapy	1.10 (1.00,1.21)
Gender	
Male	Ref
Female	0.91 (0.85,0.98)
Site	
Oesophageal	Ref
Gastric	0.89 (0.83,0.96)
Comorbidities	
Cerebrovascular disease	0.99 (0.83,1.19)
Chronic pulmonary disease	0.91 (0.81,1.03)
Congestive heart disease	1.14 (0.94,1.40)
Diabetes	1.08 (0.97,1.22)
Myocardial infarction	1.05 (0.85,1.28)
Peptic ulcer disease	0.73 (0.61,0.89)
Peripheral vascular disease	1.06 (0.89,1.26)
Renal disease	1.15 (1.00,1.33)
Liver Disease	0.82 (0.44,1.53)
Other medication use	
Statin	Not shown[a]
Aspirin	Not shown

[a] Hazard ratios for statin and aspirin use are not shown as our protocol states these are to be published separately.

Appendix 4: Negative control analysis for ACE inhibitor use and gastro-oesophageal cancer mortality

	N	Person-Years	Deaths	Unadjusted HR	Adjusted HR[a]	Trend P-value
Gastro-oesophageal						
Never	4,061	7,916	2,746	Ref	Ref	0.343
Ever	1,063	2,111	599	0.96 (0.88,1.05)	0.98 (0.89,1.08)	
1-182 DDDs	384	668	234	0.86 (0.75,0.98)	0.86 (0.75,0.99)	
183-364 DDDs	189	321	131	1.03 (0.86,1.23)	1.05 (0.87,1.25)	
365-729 DDDs	188	330	119	1.15 (0.96,1.39)	1.20 (0.99,1.45)	
730+ DDDs	302	792	115	0.97 (0.80,1.17)	1.04 (0.85,1.27)	
Oesophageal						
Never	2,182	3,914	1,526	Ref	Ref	0.054
Ever	551	923	341	1.03 (0.92,1.16)	1.04 (0.91,1.18)	
1-182 DDDs	203	322	132	0.88 (0.73,1.05)	0.86 (0.71,1.03)	
183-364 DDDs	114	156	80	1.12 (0.89,1.40)	1.14 (0.91,1.45)	
365-729 DDDs	103	141	68	1.32 (1.03,1.68)	1.35 (1.05,1.73)	
730+ DDDs	131	304	61	1.10 (0.84,1.43)	1.16 (0.88,1.52)	
Gastric						
Never	1,879	4,002	1,220	Ref	Ref	0.679
Ever	512	1,188	258	0.89 (0.78,1.02)	0.92 (0.79,1.07)	
1-182 DDDs	181	347	102	0.84 (0.69,1.03)	0.85 (0.69,1.05)	
183-364 DDDs	75	165	51	0.91 (0.69,1.21)	0.93 (0.70,1.25)	
365-729 DDDs	85	189	51	1.01 (0.76,1.34)	1.06 (0.79,1.41)	
730+ DDDs	171	487	54	0.88 (0.67,1.16)	0.95 (0.71,1.26)	

[a] Adjusted for age, deprivation, year of diagnosis, cancer treatment within 6 months (radiotherapy, chemotherapy, surgery), comorbidities (cerebrovascular disease, chronic pulmonary disease, congestive heart disease, diabetes, liver disease, myocardial infarction, peptic ulcer disease, peripheral vascular disease, renal disease) and other medication use (statins, aspirin, time-varying after diagnosis)